MRC | Cognition and Brain Sciences Unit

An introduction to transcranial brain stimulation (TMS and tES)

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Outline

- **Transcranial magnetic stimulation (TMS)**
  - A brief history
  - Principles of electromagnetic stimulation
  - Physiological effects of TMS
  - TMS protocols (Single pulse, rTMS, Theta burst)
  - Examples of experimental work

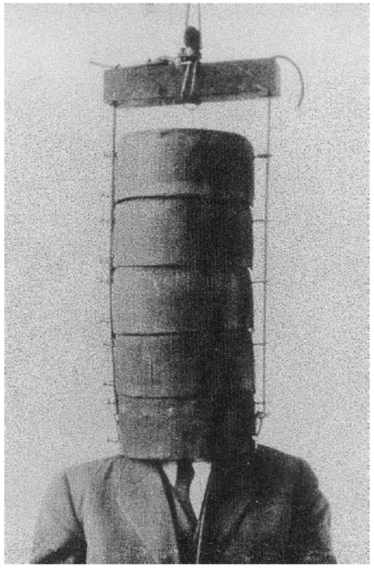
- **Transcranial electrical stimulation (tES)**
  - How does tES work?
  - Physiological effects of electrical stimulation
  - tES Protocols (tDCS, tACS, tRNS)
  - Example of tES as a scientific and therapeutic tool

Part I: Transcranial Magnetic Stimulation (TMS)

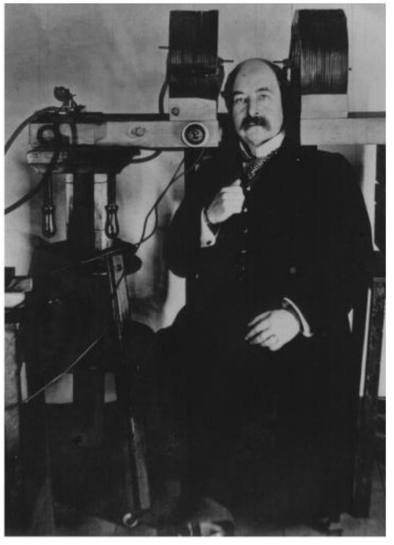
History of TMS

Electromagnetic Induction - When an electric current is turned on or off in a (primary) coil of wire, another electric current is induced in a nearby (secondary) coil by the fluctuating magnetic field around the primary coil (Faraday, 1831, 1839).

The current in the TMS coil produces a magnetic field which, if changed rapidly enough, will induce an electric field sufficient to stimulate neurons.



Magnusun & Stevens (1911; 1914)

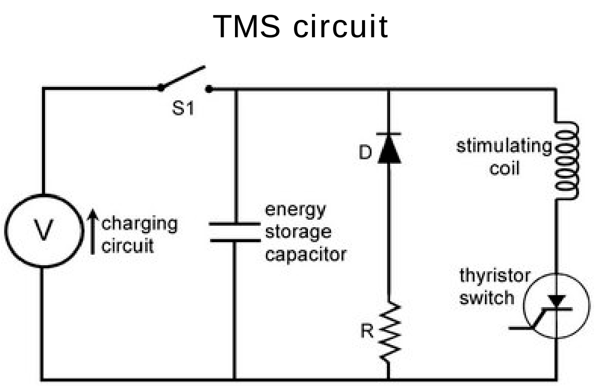


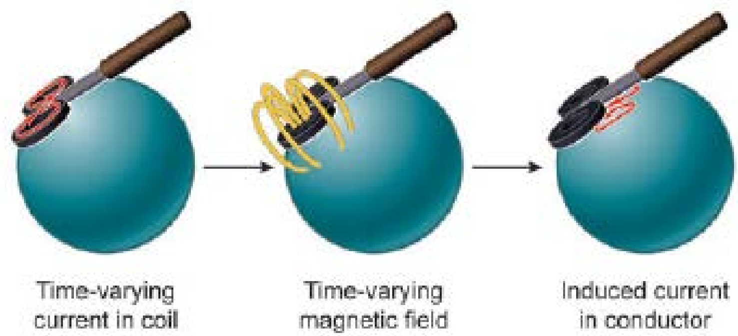
Thompson, 1910

Stimulation with magnetic fields induces phosphenes (Thompson, 1910).

TMS of motor cortex. Barker AT, Jalinous R & Freeston I. 1985. *Non-invasive magnetic stimulation of the human motor cortex*. Lancet 1:1106-1107.

What is TMS?

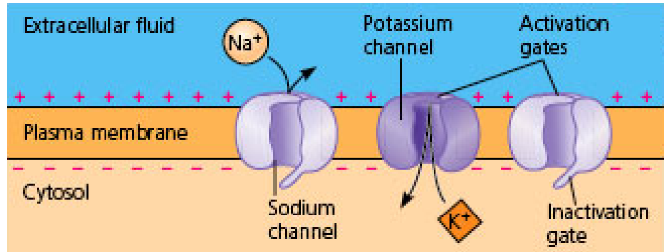




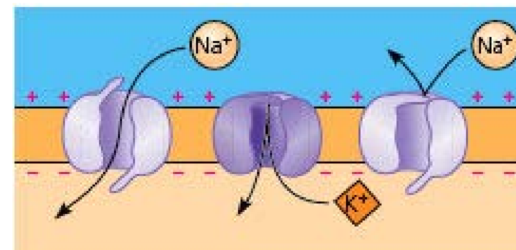
- Electric charge stored in a capacitor is discharged producing a brief, high-current pulse in a coil of wire.
- Electrical current momentarily generates a magnetic field.
- Magnetic field between 1.5T-3T and lasts approx. 100ms
- Magnetic field penetrates scalp and skull - induces a current in the brain in a direction opposite to the original current in the coil.
- More accurately – “transcranial magnetically induced electrical stimulation”

How does TMS work? – The basics - Action potentials

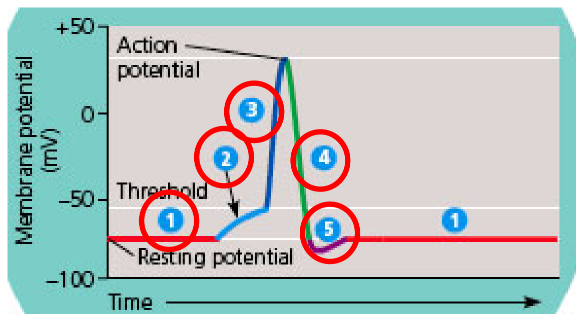
Transmission of a signal within a neuron is carried out by the opening and closing of voltage-gated ion channels.

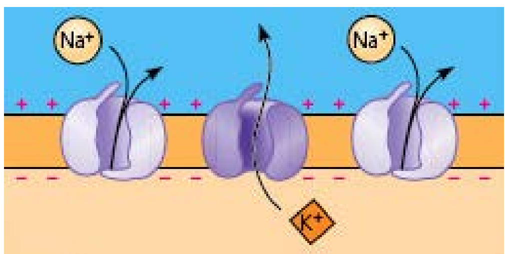


1. Resting state – membrane resting potential of -70 to -80mV

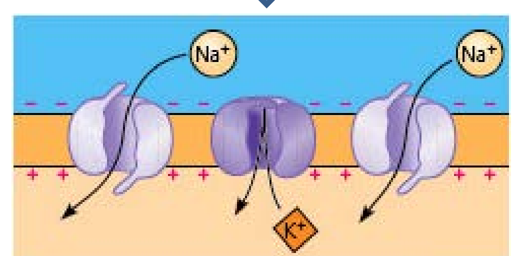


2. Depolarization – Stimulus opens sodium channels. Influx depolarizes membrane (Threshold between -55 and -50mV)

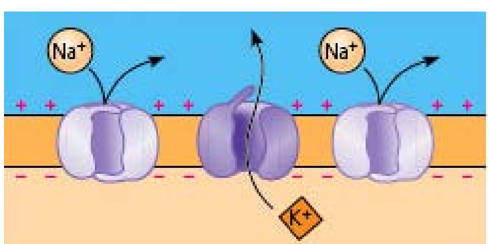




5. Undershoot - Potassium channels still open causing light undershoot. Sodium channels return cell to resting potential.

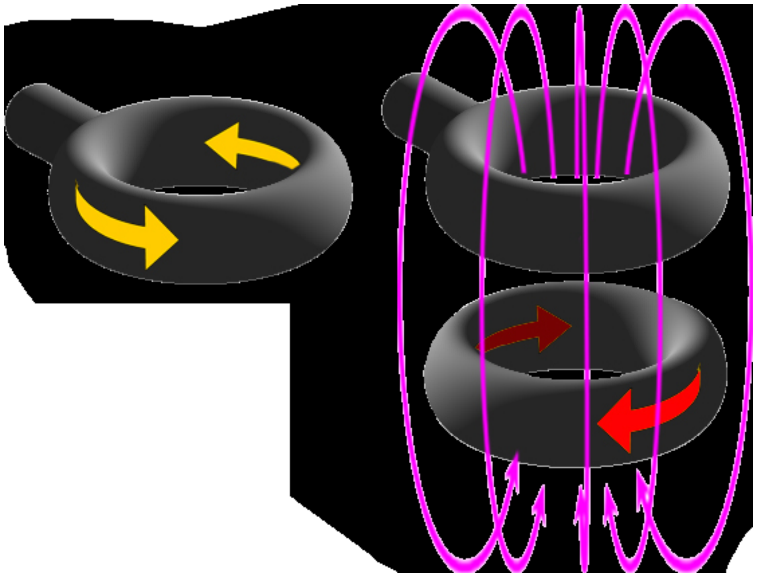


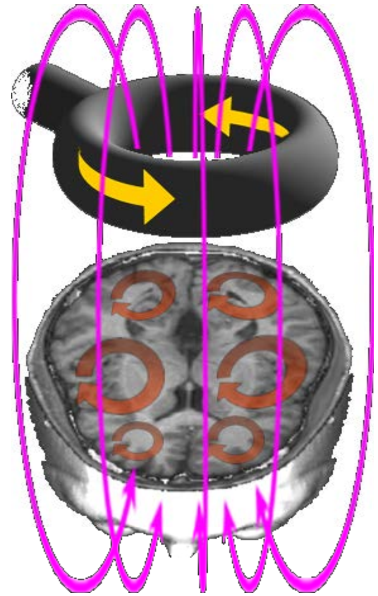
3. Rising phase – Opening of sodium channels makes inside of membrane positive with respect to outside (Potential shifts to +30 to +50mV).

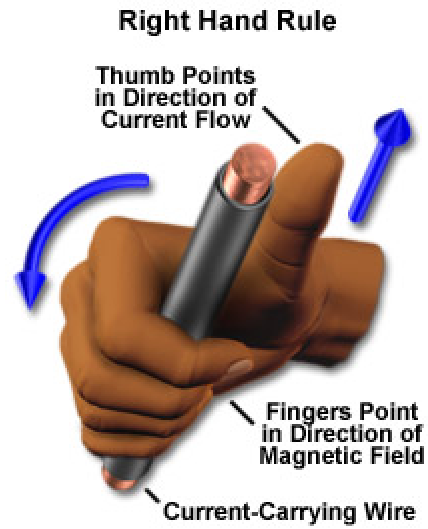


4. Falling phase - Sodium channels close. Potassium channels open. Potassium efflux makes inside of cell negative.

How does TMS work?







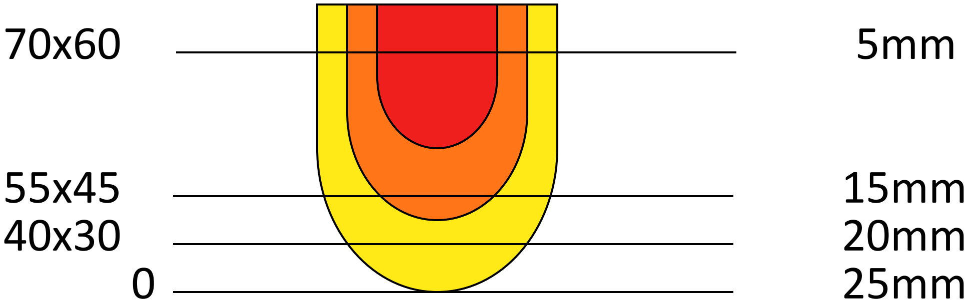
The electric field is induced perpendicularly to the magnetic field - causing ions to flow in the brain

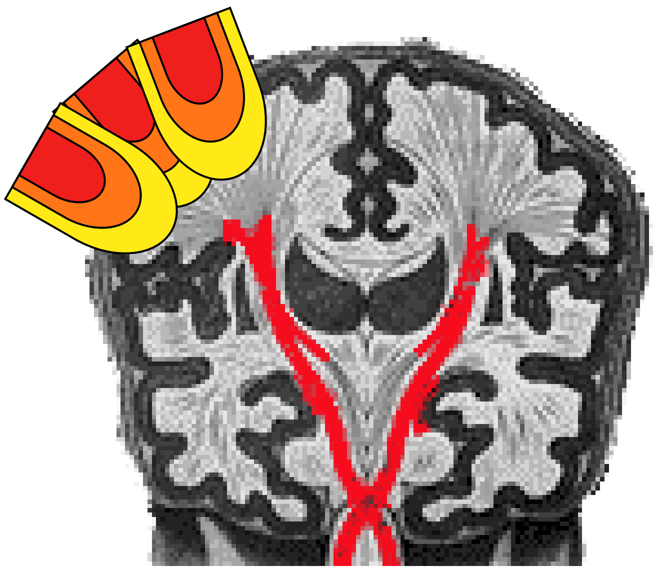
The flow of ions alters the electric charge stored on both sides of cell membranes.

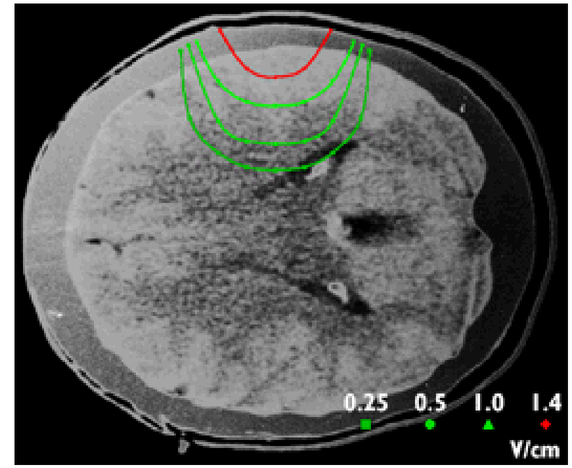
When the direction of the current is across the membrane, the induced current depolarizes cell membranes - eliciting action potentials.

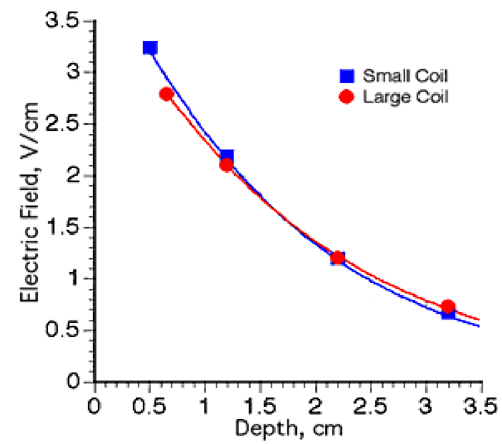
Electrical field is tangential to the scalp. TMS will most likely stimulate nerve fibers that align tangential to the scalp.

Stimulation depth









(Barker, 1999)

A depth-focality trade off - the ability to directly stimulate deeper brain structures comes at the expense of wider electrical field spread (Deng et al., 2013).

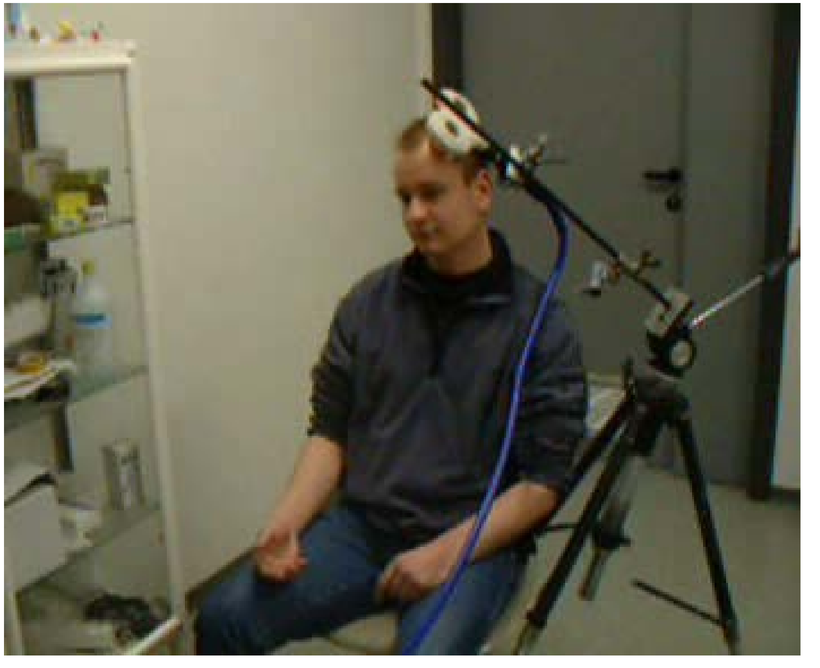
The locus of activation in the brain is approximately where the induced electrical field is maximal.

No greater than 2.5cm from the surface of the skull (Barker, 1999) . 50 TMS configurations - Ranging between 1.0–3.5 cm and 0.9–3.4 cm (Deng et al., 2013).

Effects of TMS

TMS produces different effects depending on the brain region being stimulated.

TMS can be used to produce a transient period of brain disruption - “virtual lesion”.



When applied over motor cortex, electrical impulses are sent to the peripheral nerves causing muscle twitches. Muscle contraction can be measured as a ‘motor evoked potential’ (MEP).

TMS protocols

Single pulse TMS

E.g. for mapping motor cortical outputs, studying motor conduction time – good temporal specificity - useful in targeting specific neural processes.

Paired pulse TMS (Inter pulse interval 1-100ms).

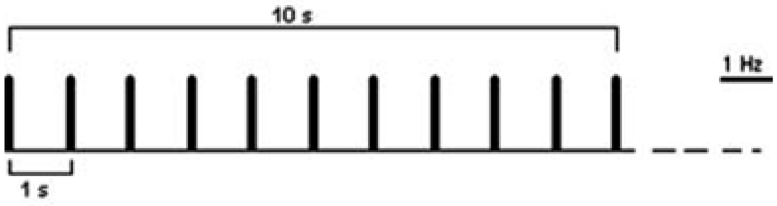
Delivered to a single target (or two different brain regions using two different coils). Cortico-cortical interactions.

Timing can be varied to selectivity stimulate inhibitory or excitatory neurons (Fitzgerald et al., 2006)
Interval of 3 ms - excitatory,
Interval of 1.5 ms - inhibitory

TMS protocols

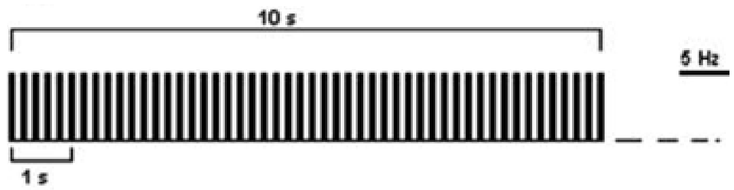
Repetitive TMS (rTMS) – Single pulse effects are not thought to last long beyond the time of stimulation (Pascual-Leone et al., 2002. rTMS generates longer-lasting changes in cortical excitability.

Low frequency rTMS (<1Hz) reduces excitability



10 s of rTMS at 1 Hz

High frequency rTMS (>5Hz) increases excitability (Padberg et al., 2007)

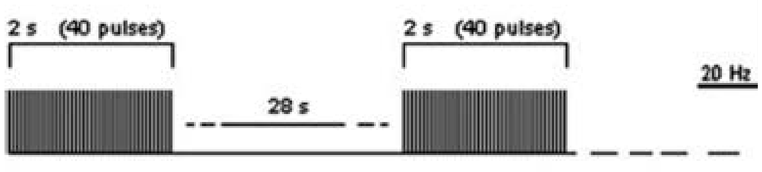


10 s of rTMS at 5Hz

TMS protocols

Patterned rTMS

Repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation



20 Hz application (trains of 2 s interleaved by a pause of 28 s)

Theta burst stimulation (TBS) (5Hz).

Based on natural firing pattern of pyramid cells in hippocampus (Kanel & Spencer, 1961) - theta-frequency pattern of neuronal firing associated with LTP.

Continuous and intermittent patterns of delivery have opposite effects on synaptic efficiency (Huang et al., 2005).

cTBS (over a period of 40s) leads to depression of cortical excitability.

iTBS leads to increase in cortical excitability.

Why use TMS?

- fMRI
  - Correlational

- Lesion Studies
  - Single or few case studies
  - Might be more than a single lesion – extend beyond area under study
  - The damaged region cannot be reinstated to obtain control measures
  - Comparisons must be made to healthy controls; no internal double dissociations
  - Given brain plasticity, connections might be modified following lesions

Why use TMS?

- Provides information about the causal role of a brain region ("virtual lesion technique")
- Can be used repeatedly in same subjects (internal double dissociations)
- High spatial and temporal resolution (although restricted to brain regions close to the skull).

Sham stimulation

- Use a control region
- Tilting coil 45° – maintains acoustic artefact and contact sensation – but still substantial stimulation (Lisamby et al., 2000)
- Sham coil – with acoustic artefact (or use masking noise)
- Experimenter is not blinded to procedure

Safety issues

Seizure induction
Single-pulse TMS has produced seizures only in patients.
rTMS has caused seizures in patients (approx 1.4%) and neurotypical volunteers (<1%).
Only one case with TBS.

TMS produces loud click (90-130 dB) in the most sensitive frequency range (2–7 kHz). rTMS = more sustained noise. Reduced considerably with earplugs.

Local pain, headache, discomfort - More common with rTMS

TMS equipment

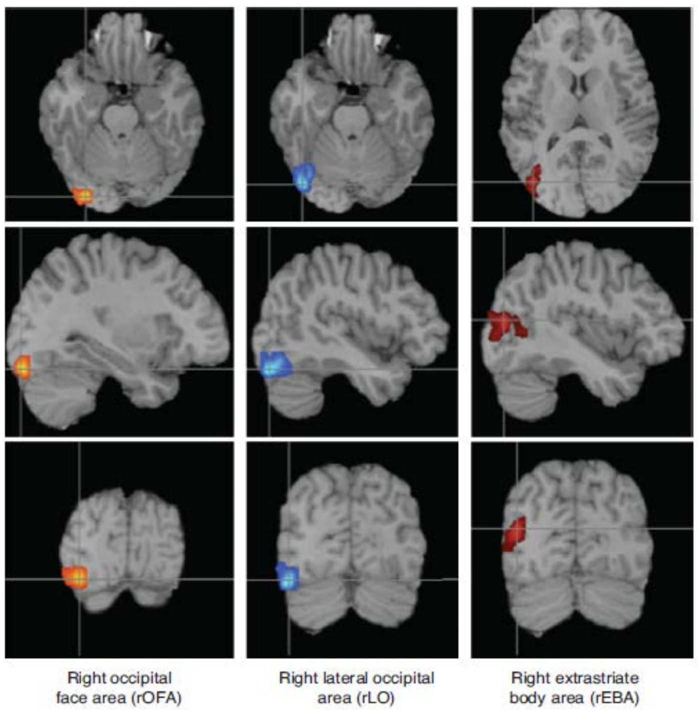
Three TMS machines at HSB:

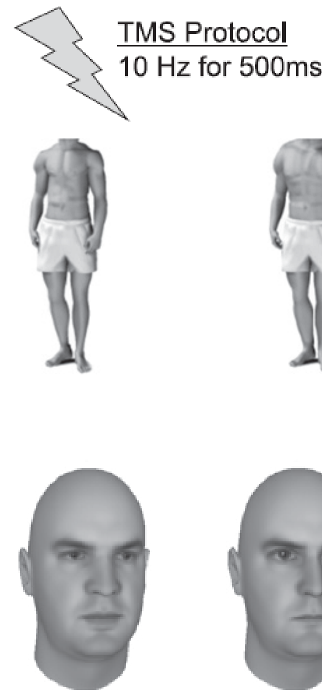
Magstim® Rapid2
Magstim® 2002
Magstim® Bistim System

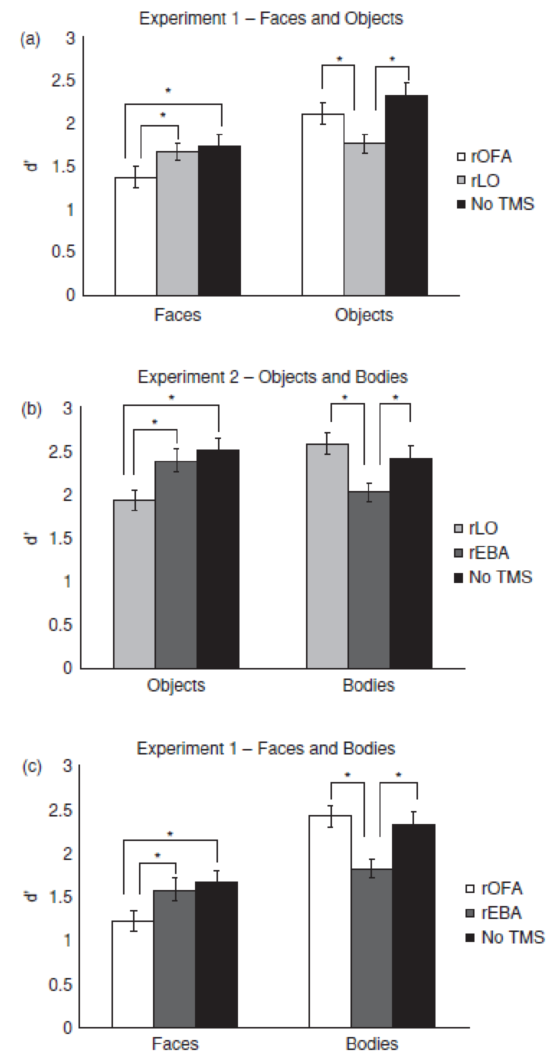
Neuronavigation software - Brainsight 2

Examples of TMS studies

TMS and category specificity in visual cortex







Regions of occipitotemporal cortex appear to be selective for faces, bodies and objects.

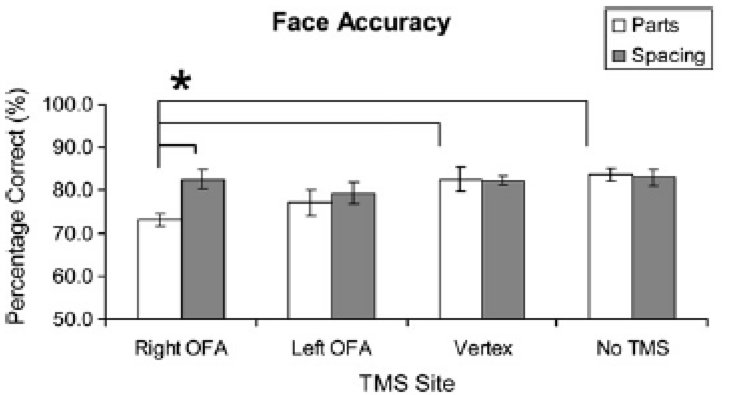
- rTMS onset concurrent with the onset of stimulus

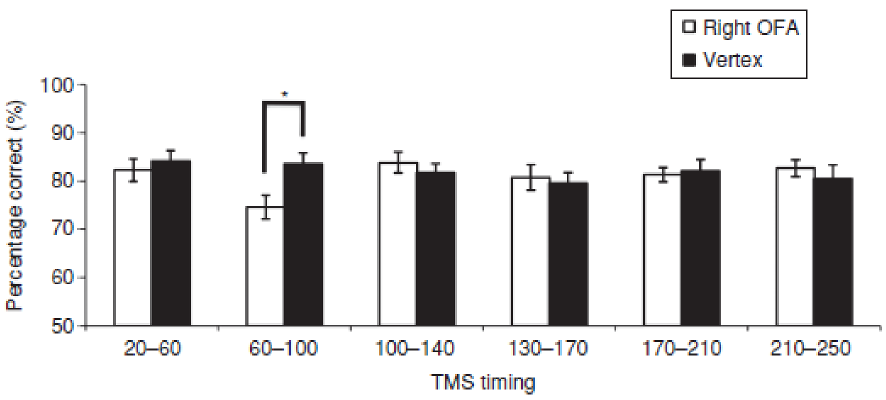
- TMS over rOFA impaired discrimination of faces but not objects or bodies
- TMS over rEBA impaired discrimination of bodies but not faces or objects
- TMS over rLO impaired discrimination of objects but not faces or bodies

Pitcher et al. (2009)

TMS and temporal aspects of face processing

Timing of face perception (Pitcher, 2007)





rTMS over OFA disrupted perception of face parts

Double pulse TMS separated by 40ms was delivered over the right OFA and vertex.

TMS to rOFA significantly affected discrimination only when delivered at 60 and 100 ms after stimulus presentation

Pulses coincided with the M100 (Liu et al., 2002).

Therapeutic use of TMS

Typical use of rTMS for treatment of depression – 20-40min, 5 days a week, 4-6 weeks.

Clinical benefits are marginal in the majority of reports

- Superiority of rTMS over a sham control, though the degree of clinical improvement is not large.
- Greater efficacy with longer treatment courses.
- Large variation in approaches (stimulation site, stimulus parameters etc) (Loo & Mitchell, 2005*).*

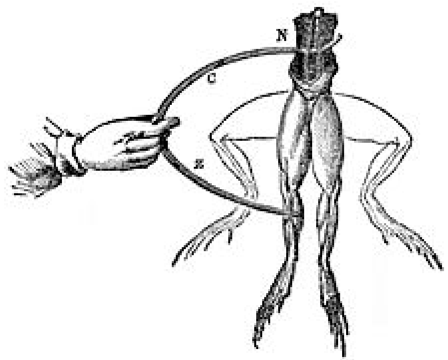
Factors: Greater response at younger age, lack of insensitivity to antidepressants, no psychotic features (Avery et al., 2008).

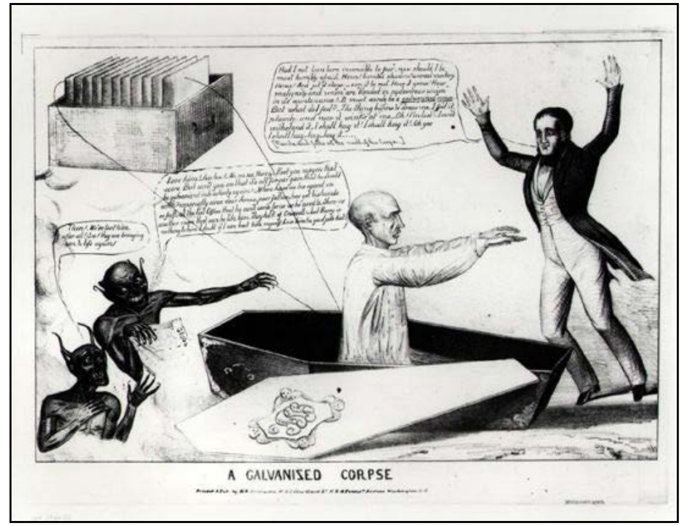
TMS Summary

- **Transcranial magnetic stimulation (TMS)**
    - Works via electromagnetic induction
    - Evokes action potentials in the brain
    - rTMS can increase or decrease neuronal excitability
    - Allows inferences about causal role of regions - “virtual lesion”
    - Excellent temporal resolution/ good spatial resolution
    - Safety/tolerance issues
    - Not easily controlled sham

Part II: Transcranial electrical stimulation (tES)

History of electrical brain stimulation





“Galvanism” - Luigi Galvani (1737-1998)

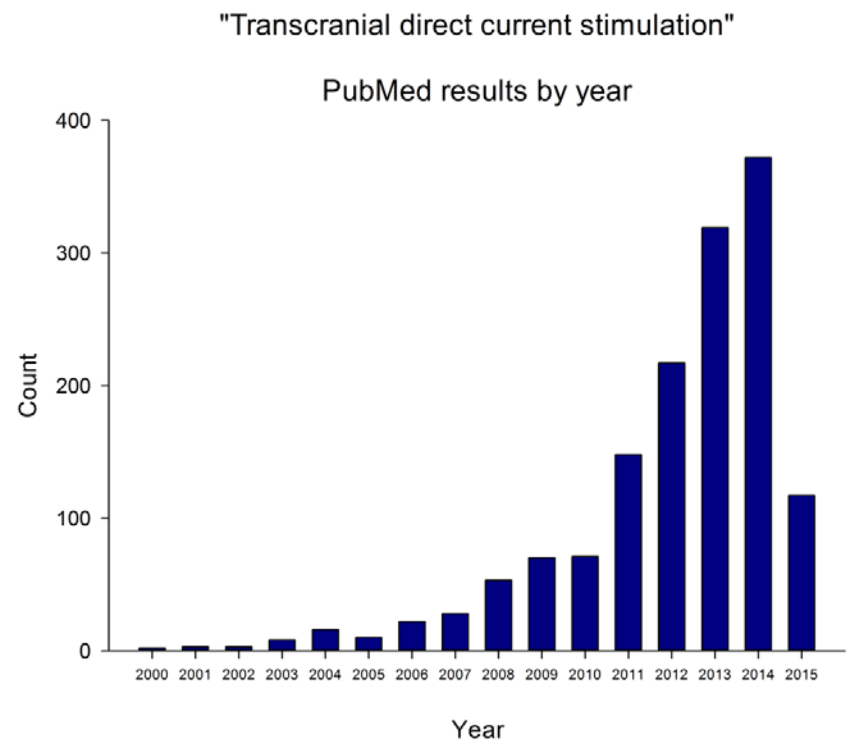
“Complete rehabilitation” of depression/psychosis following transcranial administration of electric current.

Giovanni Aldini (1804)

Electroconvulsive Therapy (ECT) (1938-)

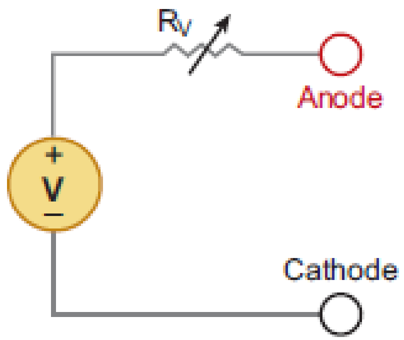
10,000 x more power than tDCS

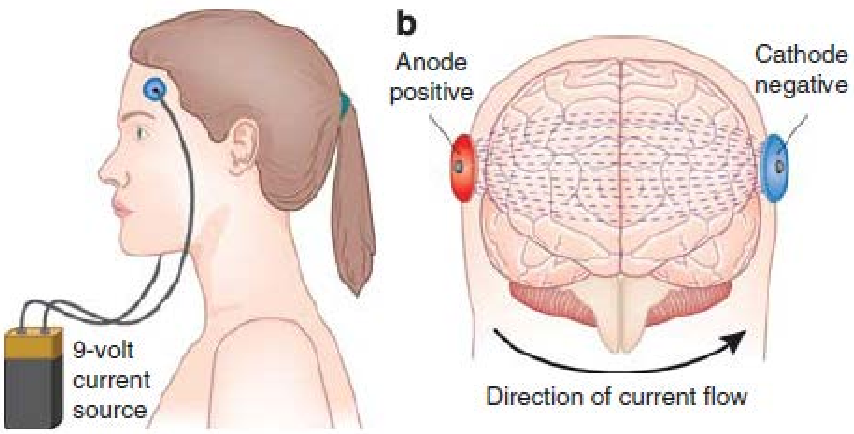
Transcranial electrical stimulation hysteria



What is tDCS?

tDCS circuit





George & Aston-Jones (2010)

A constant direct current (DC) (*i.e. a flow of electric charge that does not change direction*).

Transcranial direct current stimulation (tDCS) can induce excitation or inhibition depending on direction of current:

Anodal stimulation – excitatory
Cathodal stimulation – inhibitory

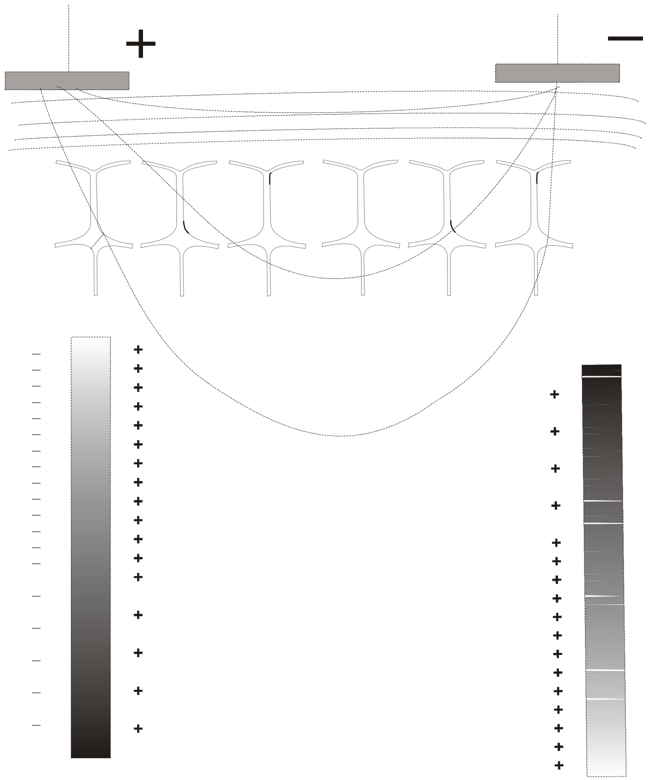
How does tDCS work?

An electric current flows between two electrodes (anodal and cathodal) on the scalp.

Part of the electric current passes through the cortex (~50%).

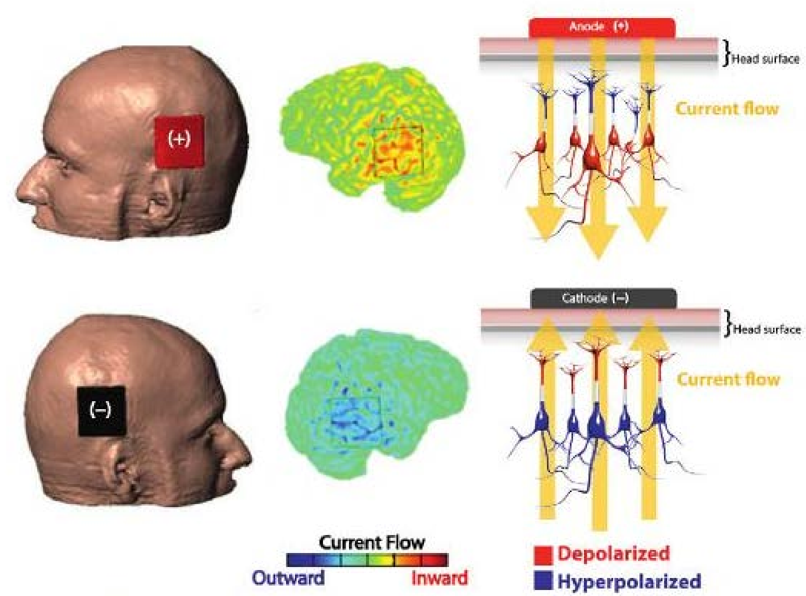
Current flow (inward) under anodal electrode induces a *lack* of positive ions (shifts membrane potential towards depolarization). - **Increases excitability.**

Current flow (outward) under the cathodal electrode induces an *excess* of positive ions (shifts membrane potential towards hyperpolarization). - **Decreases excitability**.



Depolarization of Basal membrane

Hyperpolariztion of Basal membrane



How does tDCS work?

tDCS electrical fields are far too weak to elicit action potentials:
- 2mA = ~0.3mv (15mv rest to AP threshold) – 100x weaker than TMS

Increased spontaneous firing rate (Bindman et al., 1964).

Interacts with ongoing activity (Stagg & Nitsche, 2011).

- (Rate effects) - Increase in rate of action potential generation (Carandini and Ferster, 2000)
- (Timing effects) – Change in timing of action potential (Radman et al., 2007)

How is tDCS applied?

Rubber electrodes in saline soaked sponge pads placed on the scalp.

tES studies generally use relatively-large wet sponges - from $3cm^2$ to $10cm^2$

Stimulation sites usually based on EEG electrode placement locations

currents of 1 – 2 mA

Applied for durations of up to 20 minutes.

Cathodal electrode often termed “reference electrode” – use larger size electrodes to reduced current intensity.

tDCS - neurophysiology

Acute effects are ion dependent.

- Sodium channel blocker (Carbamazepine) eliminates excitability induced by anodal stimulation during and after tDCS.
- NMDA receptor antagonist does not alter excitability changes during a short stimulation (Nitsche et al., 2003).

Long term potentiation/Aftereffects:

NMDA-receptor dependent (Fritsch et al., 2010; Monte Silva et al., 2012).

Anodal tDCS associated with reduction in GABA levels (Stagg et al., 2009). May increase glutamatergic plasticity (Ziemann et al., 1998).

tDCS – state, duration and amplitude dependent effects

State dependent effects of tDCS

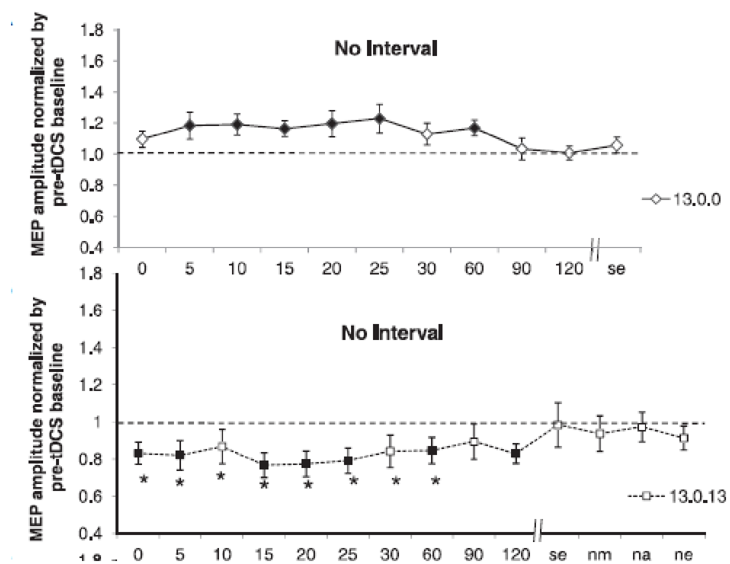
- Anodal stimulation increases excitability of motor cortex during passive condition.
- When performing a motor exercise, excitability was lower after both anodal and cathodal stimulation (Antal et al., 2007).

Non-linear stimulation intensity-dependent effects

- 1 mA cathodal tDCS decreases motor cortex excitability.
- At 2 mA, both anodal and cathodal tDCS resulted in an increase of excitability (Batsikadze et al., 2013).

Duration of stimulation.

- 13 min anodal tDCS enhances excitability for up to 60.
- Prolonging stimulation duration for 26 min converts the after-effects into inhibition.



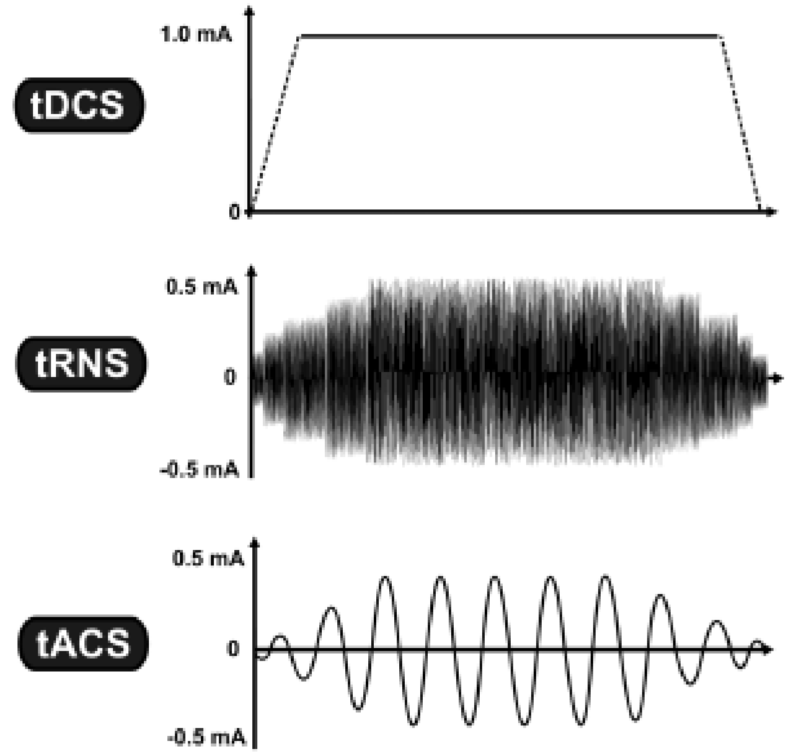
We can't assume that anodal is always excitatory and cathodal is always inhibitory.

tES protocols

Direct current stimulation (tDCS)
Application of a constant current (Nitsche and Paulus,2000)

Random noise stimulation (tRNS)
Several frequencies applied within a normally distributed frequency spectrum (0.1 to 100Hz low-frequency) (101 to 640Hz high-frequency) (Terney et al.,2008).

Alternating current stimulation (tACS)
Current is not constant (DC) but alternates between the anode and the cathode (switching polarity) with a sinusoidal waveform. Uses waveform at a specific frequency (e.g. 12Hz) (Antaletal.,2008).



Saiote et al., (2013)

tES protocols

Alternating current stimulation (tACS) –

Alternating fields can increase or decrease power of oscillatory rhythms in the brain in a frequency-dependent manner - synchronizing or desynchronizing neuronal networks.

Random noise stimulation (tRNS) –

After a depolarization, sodium channels enter an inactivated state (refractory period), but repeated stimulation may allow Na channels to be reopened in a shorter time (Schoen and Fromherz, 2008).

A DC stimulus can open Na channels just once, whereas repeated pulses (tRNS) can induce multiple ionic influxes (Terney et al., 2008).

Stochastic resonance

Amplification of subthreshold oscillatory activity - might increase neural firing synchronization within stimulated regions.

tES – Safety issues

tDCS does not cause epileptic seizures or reduce seizure threshold in animals (Liebetanz et al., 2006). No reports of seizures using tES in humans.

Slight itching or heating under the electrode - (tRNS and tACS are less easily detectable).

Headache, fatigue, and nausea only in very small minority of cases (Poreisz et al., 2007).

Safety: Cathodal can be placed on an extracephalic location (e.g. shoulder). Never place both electrodes on any other part of the body apart from the head - **currents passing across the heart can be dangerous!**

Sham stimulation
Current flow is ramped up and down for a period of 10 seconds.
Not easily detectable, doubled-blinded.

tES vs. TMS

Pros – tES easily tolerated, sham hard to distinguish, enables blinded testing, low cost, portable

Cons – Lower temporal and spatial resolution

tES equipment

Equipment at CBU:

Two stimulators on site:

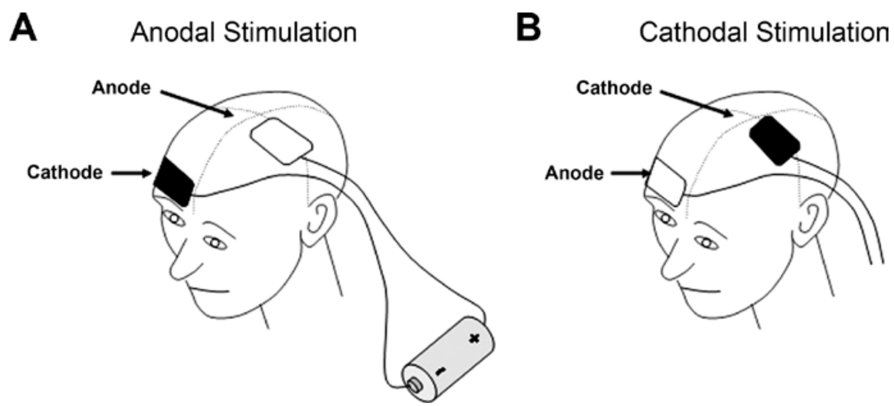
neuroConn DC-STIMULATOR PLUS
Single channel stimulator suitable for non-invasive tDCS, tACS or tRNS.

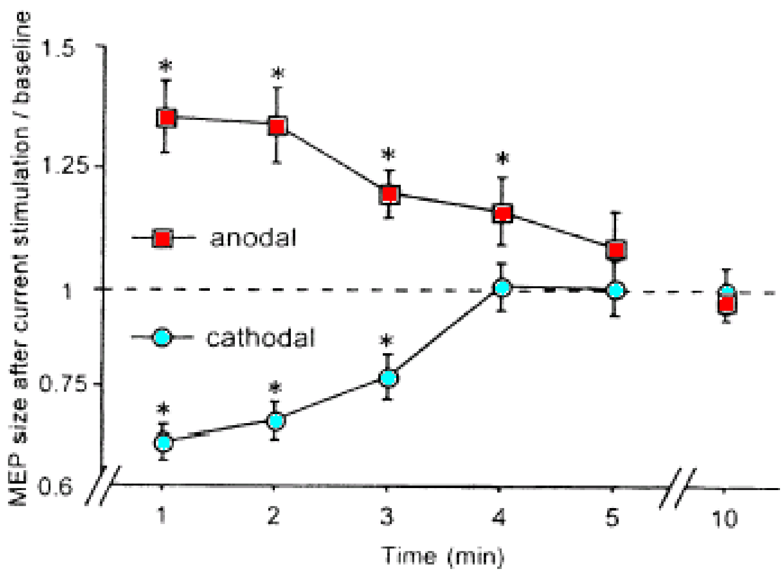
neuroConn DC- STIMULATOR MR
MR compatible version of DC-STIMULATOR PLUS.

Examples of tES studies

tES with TMS

tDCS induces excitability changes in motor cortex (Nitsche & Paulus, 2000)





Scalp tDCS stimulation (for 5 min at 1 mA).

Nitsche & Paulus (2000)

“After-effects" last up to 90 minutes after stimulation (depending on intensity and duration of stimulation)

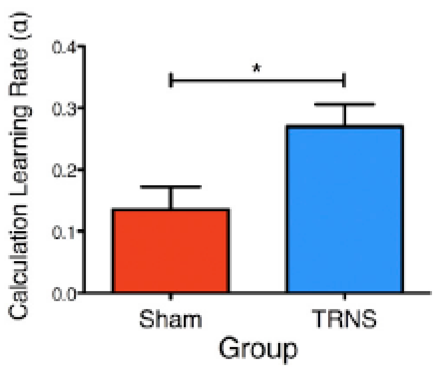
tES studies

- Working memory tasks (e.g. Ohn et al., 2008; Zaehle et al., 2011)
- Language tasks (Holland et al., 2011)
- Mental arithmetic (Cohen Kadosh et al., 2010; Snowball et al., 2013)
- Face perception (Romanska et al., in press).

- Depression in adults (Oliveira et al., 2013; Wolkenstein & Plewnia, 2013)
- Patients following stroke (Jo et al., 2009)
- Patients with Parkinson's disease (Boggio et al., 2006)
- Chronic pain conditions (Fregni, et al., 2006)
- Traumatic spinal cord injury (Fregni, et al., 2006)

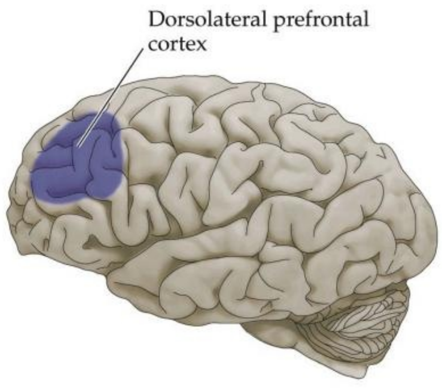
tRNS – Effects on arithemetic ability

The effect of tRNS on arithmetic performance (Snowball et al., 2013)



(Snowball et al., 2013)

Five consecutive days of tRNS-accompanied cognitive training (algorithmic manipulation)



Arithmetic performance improved following tRNS to bilateral dorsolateral prefrontal cortex.

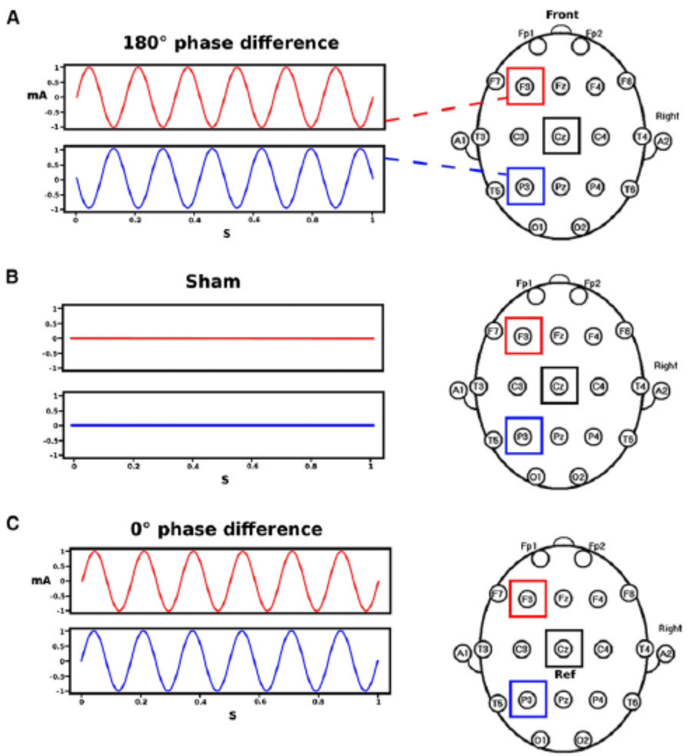
Faster learning rate in subjects receiving tRNS.

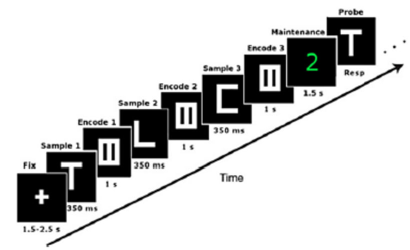
Shorter RTs for old and new (unlearned) material.

Effects persist after 6 months period

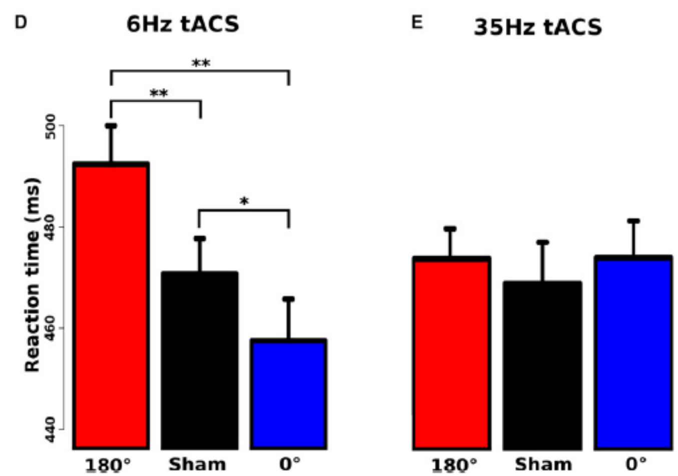
tACS – Effects of phase coupling on cognitive performance

Cortical circuits for central executive functions have been shown to emerge by theta (~6 Hz) phase coupling of cortical areas.





Subjects performed a delayed letter discrimination task.



tACS simultaneously applied at 6 Hz over left prefrontal and parietal cortex with

- Relative 0° (“synchronized” condition) phase
- 180° (“desynchronized” condition) phase
- Sham condition.

Frontoparietal theta synchronization improves visual memory-matching. Desynchronization deteriorates performance.

Evidence of causality of theta phase-coupling of distant cortical areas for cognitive performance.

Polonia et al., 2012)

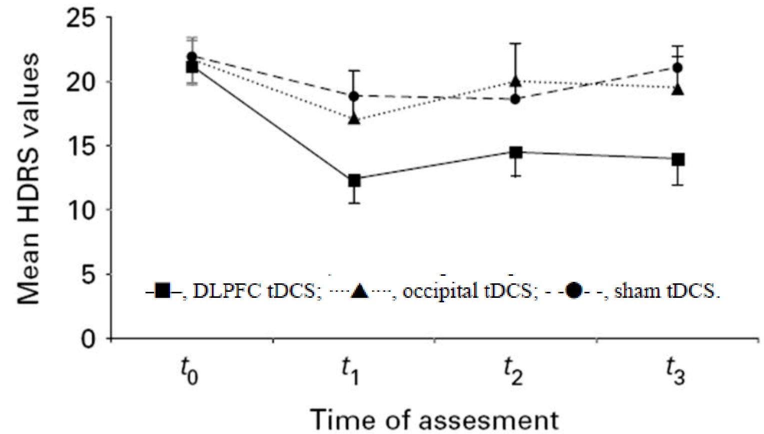
Therapeutic use of tES

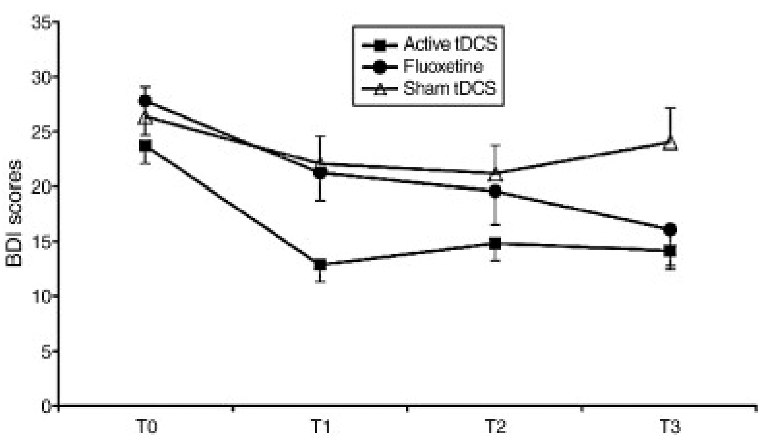
Treatment of depression

40 patients with moderate to severe major depression
- Left DLPFC (21 patients),
- occipital (9 patients)
- sham stimulation (10 patients).

- 10 sessions tDCS - 2mA

Only prefrontal tDCS reduced depressive ratings
- effects were stable 30 days later (Boggio et al.,2008).





(i) Size of clinical improvement delivered by tDCS to DLPFC similar to effects of antidepressant medication

(ii) Effects of tDCS faster than those of pharmacological treatment

(Rigonatti et al., 2008).

Summary

- **Transcranial electrical stimulation (tES).**
    - Electric current flows into brain
    -
    - tDCS shifts neuronal membranes towards (or away from) depolarization
    - Interacts with task – “neuromodulation”
    - Long term changes in learning and rehabilitation.
    - Easily tolerated
    - Well controlled sham (double blind procedure)
    - Moderate spatial resolution/ poor temporal resolution

Reading

Useful papers

Walsh V, Cowey A. (2000) *Transcranial magnetic stimulation and cognitive neuroscience*. Nature Reviews Neuroscience 1 (1): 73-80.

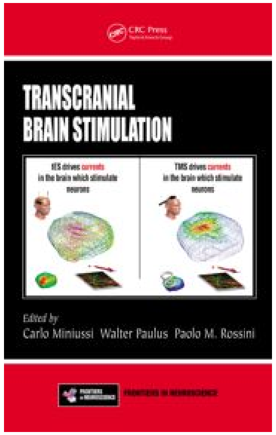
Wagner T, Valero-Cabre A, Pascual-Leone A. (2007) *Noninvasive human brain stimulation*. Annu Rev Biomed Eng 9:527–565.

Bolignini N, Ro, T. (2011) *Transcranial magnetic stimulation: disrupting neural activity to alter and assess brain function.* J Neuroscience, 30(29): 9647-50

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N et al. (2008) *Transcranial direct current stimulation: State of the art 2008*. Brain Stimul 1: 206-223

Stagg CJ, Nitsche MA. (2011) *Physiological basis of transcranial direct current stimulation*. Neuroscientist 17, (1): 37–53.

Books



Transcranial Brain Stimulation
(Edited by Miniussi, Paulus, Rossini).

Oxford Handbook of Transcranial Stimulation
(Edited by Wassermann, Epstein, Ziemann, Walsh & Lisanby).